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Translation #1059

BACTERIOLOGY. - Antimicrobian activity of chlorpromazine, antagonistic action of adenosine-5 triphosphate (ATP) and some electronic aspects of those actions. Note of Mr. Jacques Trefouel.
Compt. Rend. 255: 1155-1157, 1962.

We have studied the antimicrobian activity of chlorpromazine, which theoretical chemistry calculations represent as a strong donor of electrons, and we have shown the antagonistic action of adenosine-5 tiphosphate (ATP). Its addition to a culture of staphylococci which had been arrested by chlorpromazyne makes possible the renewal of growth. We have also shown that the lyse of the same germ by an appropriate phage, decelerated (slowed) by chlorpromazine, was accelerated by a simultaneous addition of bilfiverdine, a substance presenting the properties of a good acceptor of electrons.

Chlorpromazine is known for its numerous pharmaco-dynamic properties and notably for its action on the central nervous system. We have also described the antimicrobian activity of this substance in vitro and certain other authors consider it as an antibiotic with a bacterian spectrum of penicillin type (1).

The theoretical chemistry works show that, on the other hand, important chemical physio-chemical and biochemical properties of a substance depend on the energy values of the highest molecular orbital occupied by electrons and on the energy values of the lowest free orbital (2); those values inform us, respectively, on the ionization potential (electron donor power) and on the electro-affinity of the substance (electron acceptor power). The form of those energies is $E = \alpha + K\beta$ (2) where α and β are respectively the integral of Coulomb and the resonance integral of the molecular orbitals method. The electron donor power is greatest when the k of its highest occupied orbital is smallest and the electron acceptor power is most important when the k of its lowest free orbital is also smallest (3).

Those calculations, which were carried out by Karreman (4) for chlorpromazine, yield k values which are respectively -0,217 and -1,00; those figures show that this substance is relatively stable in its normal state and is a strong electron donor.

These new data have incited us to take up again the study of the antimicrobian action of chlorpromazine and to look for the mechanism of this action. We have used in this work the accurate technique of continual registrations of microbian growth curves with a Meci (5) electronic micro-photometer. We lack space that would be needed to expound all the results we have obtained regarding the gram-positive and gram-negative germs. We shall limit ourselves to giving here the gist of those results which concern the action of chlorpromazine on staphylococcus. With Staphylococcus Tw. and in the conditions of our experiments, we had to add chlorpromazin to the culture medium (peptonized glucosed water), with a concentration of $0.14 \cdot 10^{-3}$M, in order to put through, in the same zone of the exponential phase, the growth speed v (control sample) at v/3. In order to obtain the same result with penicillin, we had to use it at a concentration of 10^{-7}M. In that case the action of penicillin was $1.4 \cdot 10^{3}$ times stronger than that of chlorpromazine, at roughly equal molecular concentrations.

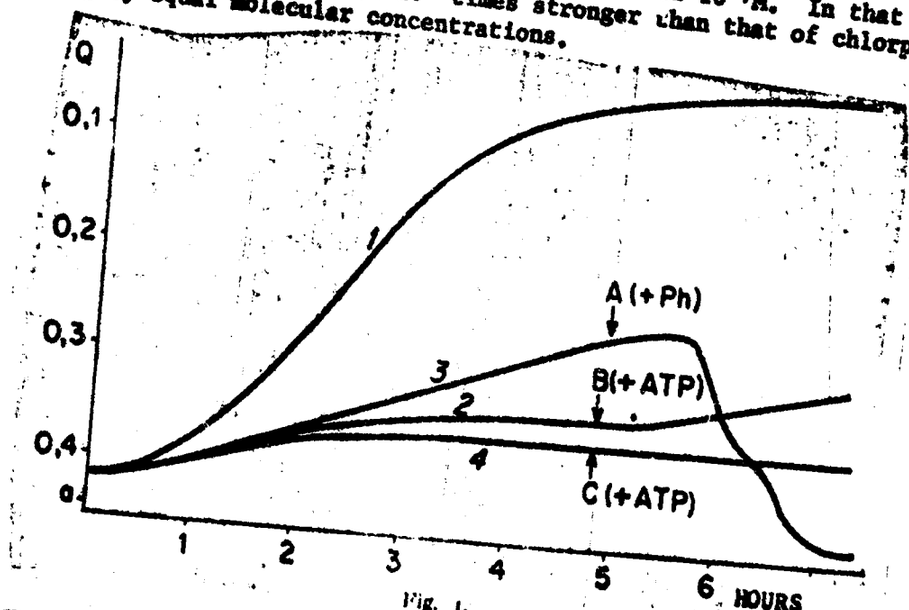

Fig. 1.

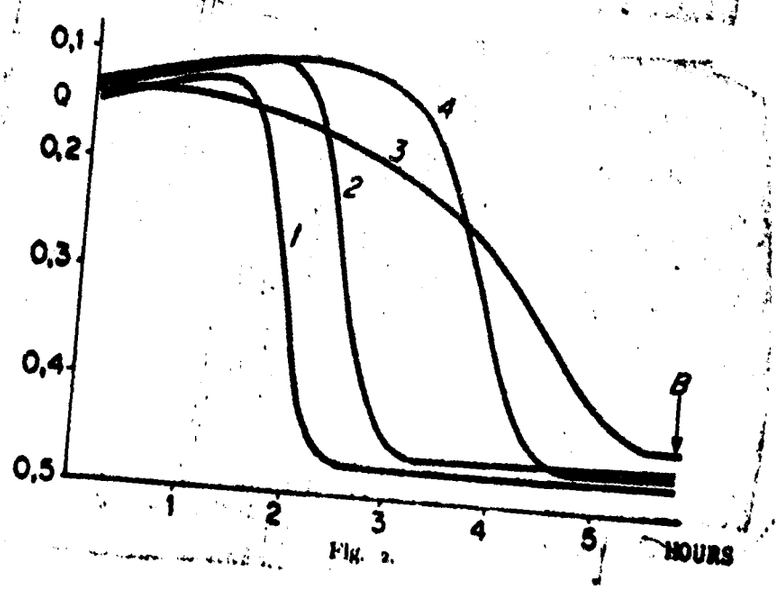

Fig. 2.

Action of adenosine-5 triphosphate. - We have studied the effect of the addition of ATP to a culture of Staphylococcus Tw. whose growth was stopped by chlorpromazine (fig. 1). Culture 3, which contains chlorpromazine at a concentration of $0.15 \cdot 10^{-3}$M and ATP at a concentration of $1.45M \cdot 10^{-3}$ at the outset, develops; however, the growth speed is inferior to that of the control sample (curve 1). Culture 2, stopped by chlorpromazine, is added, at the instant B, with ATP at a concentration of $3\ M \cdot 10^{-3}$. Growth resumes 15 to 20 minutes after this adding. Those "secondary" cultures, when ATP is added to them, remain sensitive to the appropriate phage Tw (fig. 1, curve 3). The lysis occurs about 45 minutes after adding phage.

We have noticed, on the other hand, that adding ATP to a culture of the same germ (Staphylococcus Tw.), stopped by penicillin (fig. 1, curve 4), does not cause the growth to resume. This makes it possible to think that the modes of action of penicillin and chlopromazine are not similar.

We have sought to learn the action of a good acceptor of electrons on a culture of Staphylococcus Tw., which contains chlorpromazine at a concentraion of $0,12 \cdot 10^{-3}$M and during lysis under the impact of Tw. phage. We have used biliverdin, whose k of the lowest empty orbital is +0,021 (6). The results of our experiments are condensed in the curves of figure 2, on which 1 represents the control sample lysis; 3 represents lysis in the presence of chlorpromazin, and 2 represents lysis in presence of chlorpromazin and biliverdin. The study of those curves and the titling of phages have shown that by adding biliverdin to a culture already containing a certain amount of chlorpromazine renders possible a faster lysis and a greater production of phages than in a culture with chlorpromazin alone.

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(1) J. L. Bourdon. Ann. Inst. Pasteur, 101, 1961, p. 876.

(2) B. Pullman, Chimia, 15, 1961, p.8.

(3) See B. Pullman and A. Pullman: Electronic theories of organic chemistry, Masson, Paris, 1952; B. Pullman, Acad. Roy. Belgique ("Royal Belgian Academy"), Cl. Sciences, 33,3, 1961, p. 184.

(4) G. Karreman, I. Isenberg ans A. Azent-Gyorgyi, Science, 130, 1959, p. 1191.

(5) M. Faguet. Ann. Inst. Pasteur, 97, 1959, p. 177-187.

(6) B. Pullman and A. Pullman. Results of quantum mechanical calculations of the electronic structure of biochemicals, 1, 1961, p. 704; A. Azent-Gyorgyi, Introduction to a Submolecular Biology, Academic Press, New York, 1960.

(Pasteur Institute, Bacterophagi service.)